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## Attrition-enhanced total resolution leads to homochiral families of amino acid derivatives

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

### ABSTRACT

The total resolution of five structurally similar racemizable amino acid derivatives, three of which have racemic crystal structures, was performed simultaneously. By enantioselective incorporation in an amino acid derivative that forms a conglomerate the other four were deracemized on attrition-induced grinding. The outcome of the resolution was random (*R*) or (*S*), but all compounds had the same absolute configuration and high enantiomeric purities.

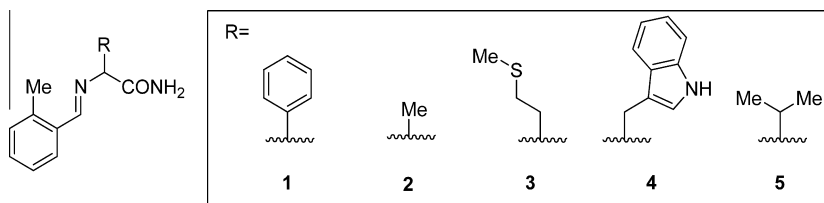
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### 1. Introduction

For some 5–10% of the time Nature ensures spontaneous symmetry breaking of organic compounds on crystallization; conglomerate structures are formed.<sup>1</sup> Occasionally these can be separated on a very small scale by hand.<sup>2</sup> Preferential crystallization has been refined to a highly usable technique to separate some conglomerates on a large scale.<sup>3,4</sup> Conglomerates that are subject to racemization have been shown to lend themselves to another technique whereby the solid in contact with solution in which racemization occurs is subjected to attrition-induced grinding under isothermal near equilibrium conditions. Under these conditions 100% yield and 100% enantiomeric excess (ee) may be achieved.<sup>5</sup>

Recently we have described<sup>6</sup> an alternative deracemization method based on the discoveries of Havinga<sup>7</sup> and Kondepudi.<sup>8</sup> A suspension of a racemic conglomerate, for example, **1** depicted in Scheme 1, is heated to dissolution (situation I in Fig. 1). Racemization in solution is catalyzed by a small amount of 1,8-diaza-

bicyclo[5.4.0]undec-7-ene (DBU). This solution is then slowly cooled to super-saturation (situation II) under abrasive grinding conditions with glass beads. The first formed crystal of, say, the (*S*)-enantiomer (situation III) is ground down to a great number of (*S*)-crystals with a relatively large crystal surface which can consume the super-saturation of the (*S*)-enantiomer in solution faster than a single crystal. The (*R*)-enantiomer, which has not yet crystallized, is converted into the (*S*)-enantiomer via racemization in solution, which results in a saturated solution of both enantiomers and crystals of the (*S*)-enantiomer hereby consuming the super-saturation of both enantiomers (situation IV). On further cooling of this mixture, more crystal mass of the (*S*)-enantiomer is generated. Without super-saturation, it is impossible for primary nucleation of the (*R*)-enantiomer to take place. This procedure results in a suspension that delivers, after filtration, enantiopure material in 76% yield. Sporadically the resolution resulted in (*S*)-**1** although in the majority of the cases (*R*)-**1** was formed.<sup>9,10</sup>



**Scheme 1.** Racemizable amino acid derivatives. It was shown that the pure enantiomers of all these compounds were completely racemized on exposure to DBU in MeCN overnight.

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We have applied this same technique to the series of amino acid derivatives shown in Scheme 1. Investigation by second harmonic generation led to the tentative conclusion that **2** is a conglomerate whereas **3–5** are racemic compounds.<sup>11</sup> Consistent with these conclusions **2** could also be readily deracemized in 75% yield and an ee of >99% using the conditions illustrated in Figure 1. On the other hand the racemic compounds **3–5** developed no measureable ee when subjected to the same procedure.

## 2. Results and discussion

Is it fundamentally impossible to deracemize a compound with a racemic crystal structure using this method? Could one devise a bypass? We considered the possibilities of co-crystallization in the crystal lattice of a conglomerate. When solutions of each of the racemic imines **2**, **3**, **4**, or **5** are mixed with an excess of **1** and the latter is crystallized from solution by the procedure shown in Figure 1, each experiment shows that **2–5** are incorporated with high enantiomeric excess into solid **1** and with the same absolute configuration (Fig. 2, experiments 1–4).

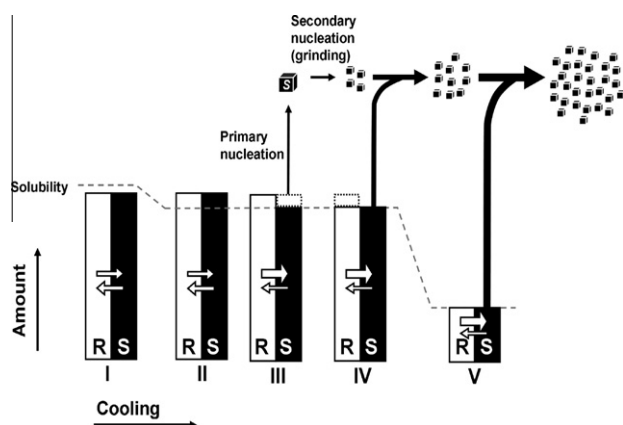


Figure 1. Havinga-Kondepudi deracemization.

When these experiments were repeated with a solution of all four imines **2–5** and with an excess of **1**, the latter is isolated with very high enantiopurity. In contrast to the abrasive grinding experiments alone,<sup>5</sup> the latter process appears to be nearly stochastic; four experiments go to (S) and six experiments go to (R). The most rewarding observation is that in the mixed experiments all five amino acid imines incorporated in the solid have identical absolute configurations although the particular configuration for the entire experiment is random as depicted in Figure 2, experiments 5–14.

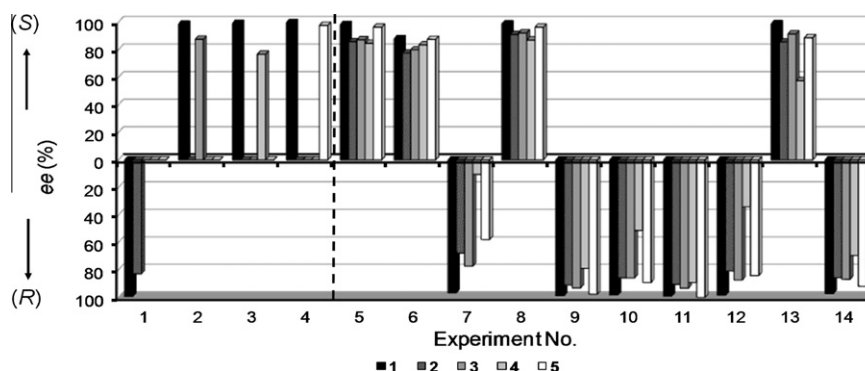


Figure 2. Enantiomeric excess of amino acid derivatives. Experiments 1–4 represent crystallizations of under-saturated separate racemates **2–5** in the presence of supersaturated racemic **1**. Experiments 5–14 represent the experiments with under-saturated mixtures of all racemates **2–5** in the presence of supersaturated racemic **1**.

The solids of experiments 5–14 were analyzed for content of imines **2–5** incorporated into the crystallized **1** and the averages of these results are given in Table 1.

Table 1  
Incorporation in the crystalline phase of **1**

Racemate	Composition <sup>a</sup> (%)	Average ee <sup>b</sup> (%)
<b>1</b>	96.76	97
<b>2</b>	0.81	86
<b>3</b>	1.22	86
<b>4</b>	0.22	66
<b>5</b>	0.98	89

<sup>a</sup> Mass percentage.

<sup>b</sup> Always in the same absolute configuration as **1**.

Although 0.29 equiv of each of the imines **2–5** have been used in comparison to **1**, only small amounts of these imines have co-crystallized. The faithfulness of recognition of family chirality is striking. It is attractive to think that this might be best realized in a solid solution. Selective incorporations have also been observed by others under non-equilibrium conditions.<sup>12,13</sup>

Since **2** is also a conglomerate, an obvious question is whether it also can incorporate other amino acid derivatives with the same stereoselection. An experiment similar to that described above was performed with an excess of racemic **2** and 0.047 equiv of each of the other imines (**1**, **3–5**). The composition of the isolated material of a single experiment is shown in Table 2. Analogous to the co-crystallization with **1** in Table 1, all components that co-crystallize in the crystal lattice of **2** do so with the same absolute configuration although it is surprising that conglomerate **1** is incorporated with the lowest ee. The incorporations in conglomerate **2** are significantly higher than those in conglomerate **1**.

Table 2  
Incorporation in the crystalline phase of **2**

Racemate	Composition <sup>a</sup> (%)	ee <sup>b</sup> (%)
<b>1</b>	0.67	36
<b>2</b>	93.53	96
<b>3</b>	2.24	73
<b>4</b>	1.94	74
<b>5</b>	1.62	75

<sup>a</sup> Mass percentage.

<sup>b</sup> All compounds co-crystallized in the (S)-enantiomer.

In both experiments, the average ee of each of the components is high,<sup>14</sup> however, the compounds that are poorly incorporated (**4** in Table 1 and **1** in Table 2) have low ees. A possible explanation is

that small amounts of remaining (racemic) mother liquor lower to a larger extent the crystal ee of the component that is incorporated the least.

### 3. Conclusion

We have demonstrated here that homochiral families of amino acid derivatives can be formed by co-crystallization with conglomerates. Although the details of the crystallization process remain to be established it is clear that these observations can serve as a model for how symmetry breaking directly coupled to formation of homochiral families might have developed in Nature. In this respect we note the recent work of Raval et al., who demonstrated how small amounts of a foreign enantiomer can be incorporated in a chiral lattice of the same absolute configuration.<sup>15</sup>

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### References

- Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Krieger: Florida, 1994.
- Pasteur, V. *The Asymmetry of Natural Occurring Compounds* (two lectures given to The Chemical Society of Paris, 1860), translated by Richardson, G. M. In *The Foundations of Stereochemistry*; American Book Company: New York, 1901.
- Coquerel, G., *Topics in Current Chemistry*, 269, *Novel Resolution Methods*; Springer: Berlin, Heidelberg, New York, 2007.
- Leeman, M.; Querniard, F.; Vries, T. R.; Kaptein, B.; Kellogg, R. M. *Org. Process Res. Dev.* **2009**, 16, 1379–1381.
- (a) Noorduyn, W. L.; Izumi, T.; Millemaggi, A.; Leeman, M.; Meekes, H.; Van Enckevort, W. J. P.; Kellogg, R. M.; Kaptein, B.; Vlieg, E.; Blackmond, D. G. *J. Am. Chem. Soc.* **2008**, 130, 1158–1159; (b) Noorduyn, W. L.; Meekes, H.; van Enckevort, W. J. P.; Millemaggi, A.; Leeman, M.; Kaptein, B.; Kellogg, R. M.; Vlieg, E. *Angew. Chem., Int. Ed.* **2008**, 47, 6445.
- van der Meijden, M. W.; Leeman, M.; Gelens, E.; Noorduyn, W. L.; Meekes, H.; van Enckevort, W. J. P.; Kaptein, B.; Vlieg, E.; Kellogg, R. M. *Org. Process Res. Dev.* **2009**, 13, 1195–1198.
- (a) Havinga, E. *Chemisch Weekblad* **1941**, 38, 642; (b) Havinga, E. *Biochim. Biophys. Acta* **1954**, 13, 171.
- Kondepudi, D. K.; Kaufman, R. J.; Singh, N. *Science* **1990**, 250, 975.
- This preference for (R)-**1** was also observed in our work concerning the deracemization of **1** by Ostwald ripening where (S)-**1** was never the product after completion of the deracemization.<sup>5</sup> It was suggested that small amounts of an (S)-additive 'steered' the resolution toward the (R)-enantiomer by blocking the growth of the (S)-crystal. This is known as the 'rule of reversal'.<sup>10</sup>
- Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* **1982**, 104, 4610.
- The conglomerate behavior of both **1** and **2** was further substantiated by formation of saturated solutions of enantiomerically enriched material (not enantiopure) in contact with solid without racemization catalyst. The mother liquor with eutectic composition was entirely racemic as expected for a conglomerate.
- (a) Kojo, S.; Tanaka, K. *Chem. Commun.* **2001**, 1980–1981; (b) Kojo, S.; Uchino, H.; Yoshimura, M.; Tanaka, K. *Chem. Commun.* **2004**, 2146–2147.
- Garcia, C.; Collet, A. *Tetrahedron: Asymmetry* **1992**, 3, 361–364.
- These experiments were carried out overnight and worked up the next morning without checking the deracemization in the solid phase. The ee of the excess conglomerate should become 100% upon prolonged stirring as a result of Ostwald ripening.<sup>5</sup>
- Liu, N.; Haq, S.; Darling, G. R.; Raval, R. *Angew. Chem., Int. Ed.* **2007**, 46, 7613–7616.